Reviewer's report

Title: Immunohistochemical study of N-epsilon-carboxymethyl lysine (CML) in human brain: relation to vascular dementia

Version: 1 Date: 10 April 2007

Reviewer: Geert Jan J Biessels

Reviewer's report:

General

This study addresses a potentially interesting topic. There are, however, major problems related to this paper. The principal aims are not adequately defined. This also applies to the study population and the principal outcome measures and other relevant variables. Furthermore, the authors apply an extensive series of statistical analyses on a relatively small patient population. This will lead to both type 1 and type 2 statistical errors. No solid conclusions can be drawn from this paper in its present form.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The aims of the study need to be clearly defined and the design of the study and analyses have to be modified accordingly.

Regarding the aims the paper currently states:

Abstract: “We tested if AGEs accumulate in the brain in vascular dementia.”
Introduction p 5: “Our present aim was to test if CML expression in the brain in elderly subjects with cerebrovascular disease relates to cognitive dysfunction.”
Discussion p14: “The main goal of our study was to test the hypothesis of a relationship between expression of RAGE ligands in cerebral vessel walls and vascular dementia.”

2. The study population needs to be defined:
Introduction p 5: “elderly subjects with cerebrovascular disease ...... people with cerebrovascular disease with or without dementia.....”
What is meant by these statements? The supplementary table list vascular abnormalities in the brain of these people, but what were the actual inclusion and exclusion criteria. What was the dementia type in these individuals? The abstract refers to vascular dementia. However, the proportion non-demented versus demented individuals is highly atypical if patients with Alzheimer’s type dementia are indeed excluded.

3. The outcome measures need to be defined more clearly.
The introduction addresses AGEs in relation to microvascular damage. In the methods section the authors describe the sampling of 10 “vessels” in the white matter and the basal ganglia. What kind of vessels?

4. The results section is rather unorganized.
p12 includes a section with the header: “Cortical neuronal CML staining: CAMCOG scores and hypertension”, p 13 with “Dependence of CAMCOG scores on pathology”. The first section deals with CML staining and dementia, the second with the actual CAMCOG scores. If CML staining is related to dementia its relation with CAMCOG scores is not so surprising.

5. Methods: the mean delay to autopsy is very long.

6. The statistical analyses are unfocussed. The number of tests and number of co-variates that is entered in these tests exceeds what is permitted for such a small population.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author
1. What is meant by survival on p 13

Discretionary Revisions (which the author can choose to ignore)

**What next?:** Reject because scientifically unsound

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'